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RESEARCH ARTICLE

Systemic inflammation response index and aggregate inflammation systemic index in male and female cancers: Implication for gender based immunotherapy

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ABSTRACT

Background: Several blood cell ratios have emerged as easy and minimally evasive inflammatory markers of cancer progression and management. Systemic inflammation response index (SIRI) and aggregate inflammation systemic index (AISI), which are reliable indicators of inflammation because they are calculated using more than two immune cells, have not been widely studied. The present study is particularly important in delineating gender-based cancers and to suggest inflammation based therapy.

Methods: SIRI and AISI were calculated from differential white blood cell counts using automatic hematology analyzer in 50 cervical patients, 50 prostate cancer patients and 61 corresponding controls.

Results: Mean values of SIRI and AISI were significantly raised in cervical cancer patients and prostate cancer patients compared with corresponding control. The mean white blood cell and neutrophil counts were significantly raised while SIRI, monocyte counts and AISI were significantly reduced in prostate cancer patients compared with cervical cancer patients.

Conclusions: This study suggests that inflammation is a phenomenon in cervical- and prostate- cancer patients but the impact of inflammation might be more in cervical cancer patients, suggesting that sex hormones might limit the efficacy of broad spectrum single cancer immunotherapy for both sexes.

Keywords: cancer immunotherapy, gender medicine, immune checkpoint inhibitors, inflammation

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INTRODUCTION

Cancer is the most common non-communicable disease and approximately one-third of cancer is preventable, another third are potentially curable if detected early and the remaining third are incurable but managed with palliative care to improve the quality of life [1]. The present study is set to find out if the same inflammation based strategy could be used in the management of male and female cancers. There are demonstrable disparities in incidence, malignancy and mortality between male and female cancers. These sex differences of cancer are important in the management of the disease, thus studies that investigates the role of sex and gender are becoming extremely urgent. The gender incidence of cancer, male-to-female ratio of 1:3 was noted in a study [2] and this was consistent with a similar study conducted by [3] in Ibadan and Abuja, Nigeria who reported male:female ratio of 1:2 in both centers. The combined age-standardized rates for all cancers in males and females were 55.8 and 189.9/100 000, respectively [3]. Breast cancer and cervical cancer are the most common female cancers, but cervical cancer is the major cause of death in women of reproductive age while prostate cancer was the most common for men [4]. Thus, our choices of cervical cancer and prostate cancer patients for this present study.

Studies on cancer patients outside Nigeria showed that for most types of

Table 1. Mean±SD of SIRI & AISI in prostate cancer patients & cervical cancer patients compared with corresponding controls

Variable	Prostate cancer (n=50)	Control (n=32)	Cervical cancer (n=50)	Control (n=29)
SIRI	0.32±0.26*	0.13± 0.12	3.20±2.32*	2.03± 2.10
AISI	96.03±21.30*	52.98±19.00	970.70±328.60*	466.40±292.80

Note. SIRI: Systemic inflammation response index & AISI: Aggregate inflammation systemic index

Table 1. Mean immune cell counts, SIRI, & AISI in prostate cancer patients compared with cervical cancer patients

Variable	Prostate cancer (n=50)		Cervical cancer (n=50)		T	p
	Mean	Standard deviation	Mean	Standard deviation		
WBC	10.28	9.74	6.27	3.11	2.264	0.027*
NEUT	9.31	5.76	4.21	2.71	1.991	0.050*
LYM	3.69	2.99	4.52	4.06	0.858	0.394
MONO	0.18	0.17	0.89	0.23	3.307	0.002*
PLT	273.76	211.82	235.72	114.1	0.713	0.478
SIRI	0.32	0.26	3.20	2.32	1.800	0.076*
AISI	96.03	21.30	970.7	328.6	15.47	0.000*

Note. WBC: White blood cell×10^9/L; NEUT: Neutrophil×10^9/L; LYM: Lymphocyte×10^9/L; MONO: Monocyte×10^9/L; PLT: Platelet×10^9/L; SIRI: Systemic inflammation response index; & AISI: Aggregate inflammation systemic index

cancer, males show a higher risk of malignancy and worse prognosis than females [5]. Males have an almost double risk of mortality for all malignancies compared to females, particularly for larynx, esophagus, bladder and lung cancers [6]. This higher mortality for the male population reflects not only the differences in the etiology of cancer but also the sexual differences in hormonal regulation and immune system function [7]. Females have stronger innate and adaptive immune responses than males, therefore reducing the risk of cancer mortality. These differences are due to epigenetic and genetic factors, sex hormones, psychosocial factors among others [8]. Cancer in females evade host immune surveillance mechanisms and undergoes a more intense immune-editing process to become metastatic and less immunogenic to exhibit resistance to immunotherapy [9]. Since inflammation was reported to determine the efficiency of immunotherapy [10], the present study provides the status on inflammation in sex-specific cancers to give additional basis for differential immunotherapy, which was hypothesized for gender based cancers.

METHODOLOGY

Prostate and cervical cancers were diagnosed using clinical and laboratory investigations by medical consultants in radiation oncology department, University College Hospital, Ibadan, Nigeria. Age-matched corresponding controls were recruited from staff and students at University of Ibadan, Nigeria. Also, informed consent was obtained from each study participant before enrolment into the study. Venous blood sample (5 ml) was collected from each study participant, dispensed into tube containing anticoagulant and blood cells (lymphocyte, monocyte, neutrophil, and platelets counts) counted using hematology auto analyzer (Sysmex XN-450). Systemic inflammation response index (SIRI) was calculated by multiplying the number of neutrophils with that of monocytes and dividing the product by the number of lymphocytes. Aggregate inflammation systemic index (AISI) was calculated by multiplying the number of neutrophils, monocytes and platelets and dividing the product by the number of lymphocytes [11].

Statistical Analysis

Data were analyzed using SPSS statistical software, version 23.0. Results were presented as mean±standard deviation [SD]. Differences in the mean levels of the parameters were determined using the student's t-test. p-values ≤0.05 were considered as statistically significant.

RESULTS

Mean values of SIRI and AISI were significantly raised in breast cancer patients and prostate cancer patients compared with controls (**Table 1**). In **Table 2**, the mean white blood cell (WBC) and neutrophil counts were significantly raised while SIRI, monocyte counts and AISI were significantly reduced in prostate cancer patients compared with cervical cancer patients.

DISCUSSION

Systemic inflammation was shown to contribute to cancer development and progression, but the exact mechanism is not clear. Nevertheless, it is thought to involve oxidative stress factors and hypoxia [12]. The results of present study suggested the involvement of immune cells especially monocytes and neutrophils as reported in our

previous studies [13, 14]. Systemic inflammatory indices derived from complete blood counts including the neutrophil:lymphocyte ratio (NLR), derived-NLR, platelet:lymphocyte ratio (PLR), monocyte:lymphocyte ratio (MLR), have received attention in the past despite low cost, easy accessibility, and predictive power [13-15]. But SIRI and AISI, which are more predictive of inflammation due to combination of many immune cells have not been widely used especially in delineating gender-specific cancers. SIRI is calculated by multiplying the neutrophil and monocyte counts divided by the lymphocyte count while AISI is calculated by multiplying the counts of neutrophils, monocytes, and platelets divided by the lymphocyte count. The cells involved in both AISI and SIRI calculations are critical in maintaining a well-balanced immune system and can also produce pro-inflammatory substances associated with various inflammatory diseases [16]. To this end, the increased SIRI and AISI in cervical- and prostate cancer-patients compared with their corresponding control are expected as observed in the present study. To the knowledge of the authors only one study assessed the levels of both AISI and SIRI in individuals with cancers and was conducted on a cohort of men with Sardinian ancestry [17].

Cells used for calculating SIRI and AISI contribute differently to cancer progression. Neutrophils have immunomodulatory effects by suppressing the activity of lymphocytes and T cell responses [18], promotes tumor growth, angiogenesis and metastasis [19], produces oncostatin M, hepatocyte growth factor, transforming growth factor-β, IL-8, and MMP [20], which contributes to tumor development, releases vascular endothelial growth factor, angiopoietin-1 and fibroblast growth factor-2, which are the main factors of tumor-related angiogenesis [20]. However, lymphocytes are responsible for immune surveillance [21], secrete cytokines, which inhibit tumor cell proliferation and have cytotoxic effects [22]. Platelets are important factors for thrombosis, mediate tumor proliferation, angiogenesis [23], interacts with cancer cells in the tumor microenvironment through paracrine signaling to promote tumor cell growth and survival [24]. Tumor-activated macrophages promote tumor growth, invasion and migration and induce the apoptosis of activated CD8+ T cells having anti-cancer activity [25]. In addition, the density of tumor-associated macrophages has been shown to affect tumor angiogenesis and is associated with poor prognosis [26]. Therefore, AISI and SIRI based on at least three inflammatory cells can be used to measure pro-tumor inflammation status as reported in the present study. The mean neutrophil count was significantly raised while monocyte count was significantly reduced but platelet count was not significantly raised in prostate cancer patients compared with cervical cancer patients. It is therefore possible that raised levels of tumor-promoting blood cells (neutrophils and platelets) play crucial role in the differentiation of male- from female- cancers.

The present study also assessed the values of AISI and SIRI in cervical cancer and prostate cancer patients to elucidate the possibility of gender differences in cancer management. Differentiating potential of SIRI and AISI could be based on the fact that the intensity of inflammation is different between males and females. Female hormone (estrogen) and male hormone (androgen) have been shown to exert opposite effects on B and T cells, macrophages, neutrophils, and natural killer (NK) cells [27, 28], therefore explaining reduced SIRI and AISI in prostate cancer patients compared with cervical cancer patients. This is further supported by the following previous reports, viz: Female sex hormones enhance the intracellular production of reactive oxygen intermediates (ROI), such as superoxide radicals and spontaneous apoptosis of neutrophils is markedly delayed in females compared to men. Secondly, estrogens through estrogen receptor-α increased M2 gene expression and polarization [29] while testosterone switched macrophage's phenotype towards M1 polarization [30, 31]. Macrophages can develop into M1-type (with anti-tumor function and promote Th1 response) or M2-type (with pro-tumor function and promote Th2 response) within a tumor microenvironment. The tumor infiltrating macrophages are almost all of the M2 phenotype. Thirdly, testosterone reduces platelet activation and reactivity, therefore reducing tumor promotion by platelets [32].

CONCLUSIONS

There is currently considerable interest in sex differences in efficacy of immune checkpoint inhibitors (such as PD-L1 expression) and cancer immunotherapies [10]. In immunotherapy clinical trials, women are underrepresented compared to men probably due to the fact that cyclic hormonal changes in a woman's body may influence the results of clinical trials [33]. It was previously stated that it would be wrong to assume that the results obtained on immunotherapy trials in male patients apply to female patients and vice versa [34], therefore clinical trials on cancer immunotherapy should be focused on detecting sexual differences, as the present study has detected differences in inflammation indices in male- and female-cancers. It is therefore recommended that future research should ensure improving the efficacy of immunotherapies in women, perhaps by exploring different immunotherapeutic approaches in both sexes [35]. It could be concluded from this study that different immunotherapeutic approaches are needed for the management of male- and female-cancers. Chemotherapy, hormonal-therapy, surgery, radiotherapy, and supportive care drugs are the most common methods of treatment for cancer patients in our center (Radiation Oncology Department, University College Hospital, Ibadan, Nigeria). However, certain cancer treatments increase infection risk and interfere with immune cell-numbers, functions, products, or organs of immune system [36].

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Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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